Brown and beige adipose tissues

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REVIEW | *Imaging in Metabolic Research*

Brown and beige adipose tissues: phenotype and metabolic potential in mice and men

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Chechi K, van Marken Lichtenbelt W, Richard D. Brown and beige adipose tissues: phenotype and metabolic potential in mice and men. *J Appl Physiol* 124: 482–496, 2018. First published March 16, 2017; doi:10.1152/japplphysiol.00021.2017.—With the recent rediscovery of brown fat in adult humans, our outlook on adipose tissue biology has undergone a paradigm shift. While we attempt to identify, recruit, and activate classic brown fat stores in humans, identification of beige fat has also raised the possibility of browning our white fat stores. Whether such transformation of human white fat depots can be achieved to enhance the whole body oxidative potential remains to be seen. Evidence to date, however, largely points toward a major oxidative role only for classic brown fat depots, at least in rodents. White fat stores seem to provide the main fuel for sustaining thermogenesis via lipolysis. Interestingly, molecular markers consistent with both classic brown and beige fat identity can be observed in human supraclavicular depot, thereby complicating the discussion on beige fat in humans. Here, we review the recent advances made in our understanding of brown and beige fat in humans and mice. We further provide an overview of their plausible physiological relevance to whole body energy metabolism.

brown fat; beige fat; thermogenesis; sympathetic nervous system

INTRODUCTION TO BROWN FAT THERMOGENESIS

Thermogenesis is etymologically derived from ancient Greek "thermos" and "genesis," which literally means heat generation. Although thermogenesis per se has multiple components, such as diet-induced thermogenesis, exercise-associated thermogenesis, nonexercise activity thermogenesis, shivering thermogenesis, and nonshivering thermogenesis (NST), the term is often used to represent the adaptive phenomenon of NST that evolved to facilitate the survival of species under cold temperature conditions (24). Essentially, taking place in the brown adipose tissue (BAT), NST is contingent on the accelerated substrate oxidative rate led to by mitochondrial uncoupling protein 1 (UCP1), a key molecule that uncouples fuel oxidation from ATP synthesis, resulting in the conversion of stored energy (essentially lipids) into heat (107). Indeed, it is the energy-expending potential of the thermogenic phenomenon that makes it an attractive target for combating the obesity and metabolic syndrome crisis of the 21st century.

Using in vitro approaches, it has been shown that, at the cellular level, the thermogenic process is initiated on the stimulation of the adrenergic receptors (AR) (in particular β_3-AR in rodents) that activate a signaling cascade downstream of adenyl cyclase involving cAMP-PKA-p38 MAPK (25). Activation of this pathway results in the phosphorylation of intracellular lipases, including adipose tissue triglyceride lipase (ATGL), hormone sensitive lipase, and monoglyceride lipase (87). Lipolysis of intracellular lipid pools releases free fatty acids (FFAs) that serve two functions: release the purine nucleotide-binding-mediated inhibition of UCP1 (50), and provide fuel for thermogenesis by undergoing β-oxidation (61) (Fig. 1). Besides the intracellular lipid pool, active BAT can also utilize circulating glucose, fatty acids that can be free, i.e., nonesterified FFAs (NEFA), or derived from lipoprotein lipase action on triglyceride (TG)-rich lipoproteins (TRLs), for fueling thermogenesis (6, 23, 70, 78) (Fig. 1). However, as severe thermogenic defects are observed in ATGL-deficient mice (1), intracellular lipid stores are considered to be critical for the thermogenic process in BAT. It is also suggested that glucose and NEFA extracted from circulation by active BAT are utilized for replenishing the intracellular TG stores rather than being combusted directly (23, 72, 81). Blocking lipogenesis in BAT has been shown to result in impaired adaptive thermogenesis (36).

Once activated, heat production in BAT can be maintained as long as the thermogenic stimuli and fuel remain present. Rodents are known to increase their food intake three- to

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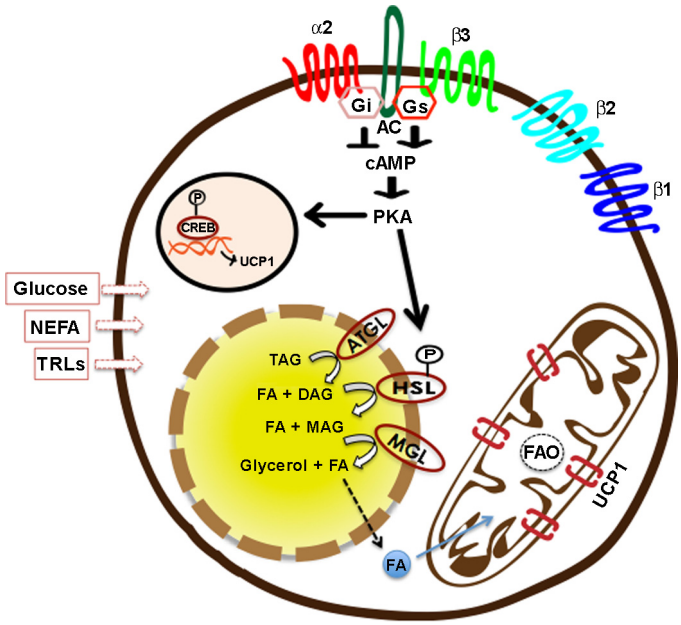

Fig. 1. Cellular events underlying UCP1-mediated thermogenesis. Adipocytes can express various adrenergic receptor (AR) subtypes (84). Whereas β-ARs ($\beta_1/\beta_2/\beta_3$) are coupled with G_s, leading to activation of adenylyl cyclase (AC), α_2-ARs coupled to G_i are inhibitory in nature. On stimulation of β-ARs, activation of G_s-AC-cAMP-PKA pathway leads to activation of UCP1 transcription on one hand, and phosphorylation of hormone-sensitive lipase (HSL) and other lipid droplet-associated proteins on the other (25). Sequential hydrolysis of triglycerides (TAG) into diacylglycerol (DAG), monoacylglycerol (MAG), and glycerol, as well as fatty acids (FAs), is achieved by enzymatic activities of adipose triglyceride lipase (ATGL), HSL, and monoglyceride lipase (MGL) (87). FAs released from intracellular lipid stores are taken up by mitochondria, where they undergo β-oxidation, and their stored energy is dissipated via UCP1 that serve to uncouple oxidative phosphorylation from ATP synthesis (23, 61). Besides intracellular lipids, brown adipocytes can also utilize circulating glucose, nonesterified free fatty acids (NEFA), and TAG-rich lipoproteins (TRLs) for fueling thermogenesis (105). Among β-ARs, β_1-ARs are often associated with an increase in proliferation and differentiation of brown adipocytes (91), whereas β_3-ARs associate with thermogenic activation (121). CREB, cAMP response element binding protein.

fourfold while attempting to maintain their body weight during chronic cold exposure. In cold-adapted rats, up to 60% of the adrenergically enhanced metabolic activity is attributable to BAT thermogenesis, pointing toward a massive thermogenic capacity of the brown adipocyte (53). This has, in turn, been associated with clearance of 50% of ingested TGs and 75% of ingested glucose, reflecting on the untapped potential of NST in burning energy substrates and, therefore, in fighting certain metabolic abnormalities (6, 105).

Although it has always been known to be present (67, 71) and to be involved in thermoregulation during neonatal stages (88), BAT in adult humans and its contribution to energy homeostasis received little to no attention for a very long time, since it was believed that BAT undergoes involution during the early years of human life (104). However, a series of important observations (40, 41, 104) that were followed by imaging studies published in 2009 changed this paradigm, by reporting its presence {identified as [^{18}F]fluoro-deoxy-glucose (^{18}F-FDG) uptake in specific areas using positron emission tomography/computed tomography (PET/CT)} in adult humans exhibiting a spectrum of age and other metabolic conditions (44, 134, 158, 165). These specific areas of metabolic activity have so far been located around supraclavicular, cervical, mediastinal, suprarenal, and perirenal regions of the human body (31, 48, 123, 158). In addition, BAT presence and thermogenic activity have been associated with lower body mass index (BMI) (158), increased insulin sensitivity (33), and improved markers of metabolic health (30, 34) in various studies, thereby highlighting its physiological relevance and underscoring the need to understand human BAT further. Here, we provide an overview of the current understanding of BAT, its subtypes, and their regulation by central and peripheral mechanisms. In addition, we have reviewed the physiological relevance of BAT as well as key issues related to the detection and utility of human BAT.

CLASSIC BAT VS. RECRUITABLE BEIGE FAT

Recent classification of BAT as the "classic BAT" and the "inducible" or "recruitable" beige fat is based on the observations made in rodents, where classic BAT is recognized as the discrete fat depots located in the interscapular, cervical, axillary, and perirenal areas that are exclusively composed of classic brown adipocytes (143). In contrast, the inducible BAT represents the white adipose tissues (WAT) that possess the ability of undergoing browning, that is, of harboring pockets of brown-like adipocytes expressing UCP1 among white adipocytes on stimulation (43, 69, 116, 180). These cells have been referred to as brite (acronym for "brown in white"), beige, or recruitable adipocytes. It is important to note that, although most WAT depots have been shown to undergo browning, the propensity of browning varies considerably among various fat depots, thereby somewhat justifying the present nomenclature. For instance, inguinal WAT (iWAT) undergoes browning to a much greater extent than what is observed for gonadal fat, e.g., epididymal WAT (eWAT) in rodents (110, 166); hence it has almost become dogmatic to identify iWAT as the beige fat depot, whereas eWAT is looked on as more of a true white fat depot (129, 138, 166, 169) (Fig. 2).

Phenotypic Features

The anatomic distinction of classic BAT vs. inducible beige fat is also retained at the adipocyte level, where a classic brown adipocyte is recognized with its signature phenotype of being multilocular and carrying numerous mitochondria, along with exhibiting significant expression of UCP1 (23, 125) (Fig. 2). In contrast, the phenotype of an UCP1-expressing cell in WAT can vary significantly based on its state of stimulation (37, 175). Under nonstimulated conditions, brite adipocytes can exhibit a unilocular or paucilocular phenotype with few mitochondria and low UCP1 expression, whereas, under stimulated conditions, brite adipocytes resemble classic brown adipocytes with their signature phenotype and significant expression of UCP1 (37, 175) (Fig. 2). Owing to this phenotypic variability, two predominant schools of thought exist regarding the origin of brite adipocytes. While some suggest that these adipocytes are derived from de novo adipogenesis of specific precursors, others propose that mature white adipocytes are capable of undergoing transdifferentiation into brown adipocytes upon stimulation (39) (Fig. 2). Lineage tracing experiments utilizing different approaches have provided evidence that, on cold exposure or adrenergic stimulation, newly developed brite cells in iWAT depot originate from de novo differentiation (171) or

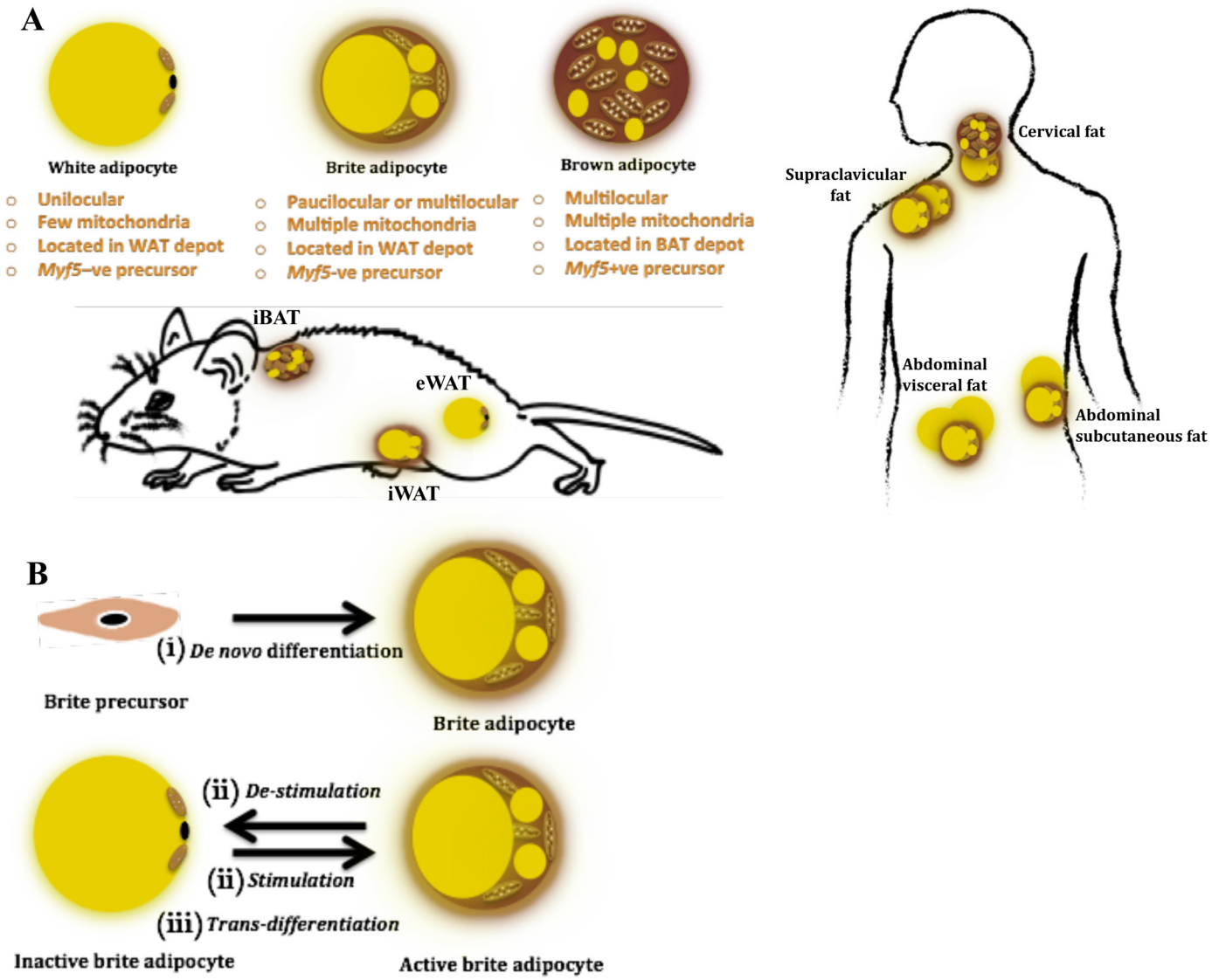

Fig. 2. *A*: characteristics, origin, and location of brown, brite, and white adipocytes in mice and men. Adipocytes can be white, brown, or brite in nature. Location-wise, deep neck biopsies from the cervical region have been reported to express classic brown markers (93, 106), whereas most studies dealing with human supraclavicular fat report a beige fat signature in this depot (46, 74, 140, 142, 175). In addition, evidence exists for abdominal visceral and subcutaneous fat depots to undergo browning in humans (54, 144). In mice, interscapular brown adipose tissue (BAT) represents the most commonly studied classic BAT depot, whereas, based on the extent of browning, inguinal white adipose tissue (iWAT) often represents a beige fat depot, and epididymal white adipose tissue (eWAT) is considered to be a true WAT depot (129, 138, 166, 169). *B*: proposed mechanisms of brite adipocyte origin. Brite adipocytes have been proposed to originate either from *i*) specific precursors via de novo differentiation (171); *ii*) mature white-looking brite adipocytes upon stimulation (129); or *iii*) from mature white adipocytes via transdifferentiation (37).

directly emerge from mature adipocytes that likely have a brite signature (91). Evidence also exists for brite cells to revert back to unilocular white-like adipocytes on the removal of thermogenic stimulus (129). It seems plausible as of now that the plasticity of beige fat depot represents the ability of a brite adipocyte to exist as an active or dormant thermogenic adipocyte (68, 76).

Ontogeny and Molecular Profile

Evidence further suggests that these two cell types exhibit different ontogeny. Whereas the classic brown adipocytes are derived from skeletal muscle-type progenitors expressing *Myf5* or *Pax7* (92, 137), brite adipocytes are *Myf5* negative and exhibit a smooth muscle cell-like origin with progenitors marked by *Myh11* (94) (Fig. 2). Efforts made in recent years to distinguish these adipocytes have also revealed molecular signatures associated with each cell type, which allow for the identification of a UCP1-expressing adipose depot as being classic brown or beige in nature (46, 74, 93, 169, 175). Assessment of these molecular signatures have further uncovered that, while markers consistent with classic BAT can be identified in the interscapular fat (in infants) and deep neck fat biopsies (46, 74, 93), the majority of cervical, supraclavicular, and mediastinal fat depots in adult humans appear to share their molecular signatures with rodent beige fat (46, 93, 106, 140, 175) (Fig. 2). Global and unbiased molecular analyses of

human supraclavicular brown fat at the single-cell resolution also revealed a molecular signature resembling that of rodent beige fat (142). Thus, unlike rodents, which exhibit clear anatomic depot segregation of classic brown and beige fat, UCP1-positive adipocytes expressing classic brown- or brite-specific markers can be located very close to each other within a given anatomic location in humans (46, 106). Developmental origins of each of these adipocytes, however, remain unknown.

Thermogenic Function

Despite the anatomical and molecular dissimilarities, a key factor that binds classic brown and brite adipocytes together is the presence of UCP1. It has been shown that UCP1 maintains its uncoupling and thermogenic ability, irrespective of its location (138). However, the relative contribution of beige fat UCP1 to total thermogenic response has been estimated at one-fifth of the classic BAT depot, owing to its quantitatively lower thermogenic density (i.e., UCP1-dependent oxygen consumption per gram of tissue wet weight measured using an in vitro approach), at least in rodents (138). It has been suggested that UCP1-independent futile cycles, such as TG/FFA cycle (52) and Ca^{2+} futile cycling (153), can contribute to enhanced energy expenditure in WAT. Of note, creatine-driven substrate futile cycling was recently identified as a significant contributor to enhanced energy expenditure in rodent beige fat during cold exposure (77). Interestingly, genes involved in creatine-driven futile cycling exhibited a compensatory upregulation in UCP1-ablated mice, whereas a reduction in creatine bioavailability was associated with lower core body temperature in these mice (77). Deep neck biopsies of human BAT were also recently shown to exhibit a proteome consistent with utilization of both coupled and uncoupled pathways for enhancing energy expenditure, in particular the observed enrichment of mitochondrial creatine kinase and interactome complex (103). Although the relative relevance of these mechanisms remains to be seen, these observations indicate that beige fat has the potential of contributing to whole body energy expenditure significantly via UCP1- and creatine-dependent futile cycles.

REGULATION OF BAT METABOLISM

Sympathetic Nervous System-mediated Regulation of Brown and Beige Fat

Physiologically, NST is under control of the central nervous system. The central nervous system, via the sympathetic nervous system (SNS), is a strict controller of BAT thermogenic activity by means of governing UCP1 expression and its activity (25), as well as the proliferation and differentiation of brown as well as brite adipocytes (91, 101). Indeed, neural centers involved in thermoregulation have been ascribed a role in the control of BAT thermogenesis. In particular, preoptic area (POA)-dorsomedial hypothalamus (DMH)-raphe pallidus pathway is known to exert central thermoregulatory control over BAT (83, 100, 124, 141). In addition, neural centers involved in the regulation of energy balance have been reported to relay to both classic BAT and WAT depots. Using pseudorabies virus (PRV)-labeled retrograde tract tracing approach, paraventricular hypothalamus (PVH), lateral hypothalamus, DMH, arcuate nucleus, and POA have been identified as relaying to BAT (5, 10). Evidence also supports a role for ventromedial hypothalamus in the SNS outflow to BAT (26). In addition, PVH, DMH, and POA have been reported to relay to WAT (7, 9). Despite an overlap among the neuroanatomical brain regions involved in the modulation of BAT and WAT depots, it is clear that downstream regulation of SNS activity at the level of neuropeptide expression, innervation, and SNS drive varies greatly at the depot level, both between BAT and WAT, as well as among various WAT depots (4, 19, 84). Indeed, the enhanced presence of PRV-labeled neurons in the DMH can be seen when PRV injection was made in iWAT relative to eWAT (4). Additionally, cold exposure has been shown to enhance SNS drive to BAT and iWAT much more strongly than to eWAT, whereas glucoprivation was associated with enhanced SNS nerve activity to iWAT selectively (19). Similarly, AR expression as the downstream mediator of SNS circuitry is known to be variable among various fat depots (84).

It is well established that adrenergic control over BAT and beige fat is mediated via ARs (Fig. 1), specifically β_3-AR in the case of rodents; β_3-AR-less mice exhibit severe thermogenic defects and lack of beige fat development on cold exposure (2, 75). In addition, β_3-AR agonism has been shown to replicate the effects of cold exposure on both brown and beige fat depots (60). Rodent adipocytes are known to express β_1-, β_2-, and β_3-ARs, where β_1-ARs are reported to be important for the proliferation of brown adipocytes (91) and β_3-ARs, largely expressed by mature adipocytes (22), are primarily responsible for mediating their thermogenic activity (121). Lack of β_1-AR is associated with inhibition of BAT hyperplasia associated with cold exposure (91), whereas β_3-AR stimulation does not induce BAT hyperplasia, despite increasing its activity, suggesting that both β_1- and β_3-AR are needed for a full thermogenic response (121). Overexpression of β_1-AR has also been associated with browning of iWAT in rodents (145). In addition, α_2-ARs, known to inhibit cAMP signaling, are known to be present in rodent adipocytes, however to a much less extent than what is seen for human adipocytes. Peripheral and central (in raphe pallidus) injections of α_2-AR agonists were recently shown to inhibit BAT thermogenesis in rats (96), indicating that α_2-AR exhibit inhibitory control over BAT thermogenesis. Emerging evidence further suggests that an interplay between the relative expression or affinities of various ARs is not only important for the thermogenic outcome in BAT, but may also influence browning of WAT depots in rodents (131). In contrast to rodents, human adipocytes predominantly express β_1- and β_2-ARs, which have also been shown to play a role in human BAT activity (115, 148). Although β_3-ARs mRNA and protein have been reported in human brown fat (165, 181), and at least one recent report indicates that β_3-AR agonist treatment can enhance metabolic activity in human BAT (45), direct evidence of major contribution of β_3-AR in the control of thermogenic activity in humans needs further elucidation (85, 135, 168) (Fig. 1).

An important question of whether a neuroanatomically distinct SNS outflow circuitry exists for the beige fat and brite adipocytes was recently addressed by Bartness and Ryu (8), where they extensively discuss the only study dealing with the issue, reporting a role for DMH-specific neuropeptide Y neurons in the sympathetic outflow to beige (i.e., iWAT and dorso-subcutaneous WAT) but not white fat (eWAT) (29). We know that, even at the maximum level of stimulation of a beige fat depot (for instance iWAT), not all adipocytes acquire a

brownlike phenotype, indicating that a mix of pure white and brite adipocytes exists in this depot at all levels of stimulation. The obvious next question thus arises as to whether specific neuroanatomic circuitry relay to brite adipocytes within a beige fat depot. Bartness and Ryu (8) suggest it to be an unlikely scenario based on the general observations that most SNS nerves innervate WAT depots in an en passant manner. Instead, they suggest, and we agree, that a combination of factors, such as differential SNS drive, stimuli-specific effects, propensity of an adipocyte to norepinephrine-mediated stimulation, either due to cell-autonomous factors, or due to AR expression, as well as their sensitivity, would contribute to the commonly observed differences among WAT depots in terms of their browning potential (8).

Sensory Control of Brown and Beige Fat

Besides SNS, investigators have looked for both parasympathetic and sensory innervation of BAT and WAT depots. Although partial evidence exists to point toward parasympathetic innervation of BAT and WAT, this idea has been challenged critically (7, 10). However, both BAT and WAT depots (including beige fat depots such as iWAT) are known to exhibit sensory innervation (132, 133, 146, 160). Using the H129 strain of herpes simplex virus and anterograde tract tracing approach, it has been shown that most areas involved in the SNS outflow to BAT and WAT, such as PVH, DMH, and lateral hypothalamus, also connect with the sensory inputs from these fat depots, pointing toward a SNS-sensory feedback loop that exists in both BAT and WAT depots (132, 133) (Fig. 3). It has been postulated that sensory nerves in BAT serve to sense its thermal status, blood flow, or intracellular lipolytic products and hence regulate its thermogenic activity via the SNS loop (10, 133). Direct BAT sensory denervation has been reported to induce BAT atrophy (160). Similarly, sensory nerves in WAT have been proposed to regulate lipolysis via sensing lipolytic products (7, 132). Of note, BAT exhibited relatively lower levels of PRV152 + H129-double-labeled neurons for SNS-sensory inputs than WAT, indicating that WAT is under a stronger sensory control than BAT (133). Nonetheless, a considerable overlap among the neural centers regulating SNS and the sensory circuitry to BAT and WAT also raises the question of whether this circuitry is built for the regulation of both the thermogenic (BAT) and lipolytic (WAT) arms of fat stores that function as part of a so-called "adipose organ" (38), such that a sensory input from WAT alters the thermogenic response in BAT and vice versa. Indeed, a recent study revealed that lipolysis as well as its products, such as FFAs eicosapentanoic acid and arachidonic acid, activate sensory neurons of iWAT, which was further associated with enhanced BAT thermogenesis in Siberian hamsters (56).

It is indeed quite clear that sympathetic outflow to WAT and BAT is concerned with differential physiological output, with SNS being the primary controller of lipolysis in WAT and that of thermogenesis in BAT (Fig. 3). Furthermore, it is also becoming clear that lipolysis and thermogenesis are tightly connected, both at the intracellular and tissue level. Within BAT, intracellular lipolysis is essential for thermogenesis, as its abrogation leads to thermogenic failure (63, 147). Our laboratory has recently shown that blocking intracellular lipolysis leads to a severely blunted metabolic response in the interscapular BAT (iBAT) in rats (81). However, it further seems that thermogenesis in BAT is also dependent on WAT lipolysis at the tissue level, with this communication being under the regulation of SNS sensory loops in both of these depots. Surgical denervation of WAT was recently shown to block increases in BAT temperature during CL316,243 infusion (56). Human studies have also revealed a direct correlation between WAT lipolysis and metabolic activity in BAT (13, 34). Often, we look at this relationship being simply about WAT lipolysis providing fuel for BAT thermogenesis. However, recent work by Garretson et al. (56) suggests that WAT can exert control over BAT beyond thermogenesis, plausibly to regulate circulating NEFA levels. Thus it is likely that any factor or physiological condition that is associated with an upregulation in WAT lipolysis without a need for increasing core body temperature may result in transient BAT activity just to ensure excess NEFA have been take care of to maintain metabolic homeostasis.

Non-SNS-mediated Regulation of Brown and Beige Fat

Besides the direct control exerted by the SNS in the modulation of both brown and beige fat activity, multiple circulating factors falling in the categories of hormones, growth factors, myokines, adipokines, and metabolites have been shown to exert control over the development as well as thermogenic activity of brown and beige fat (164). Interestingly, most of

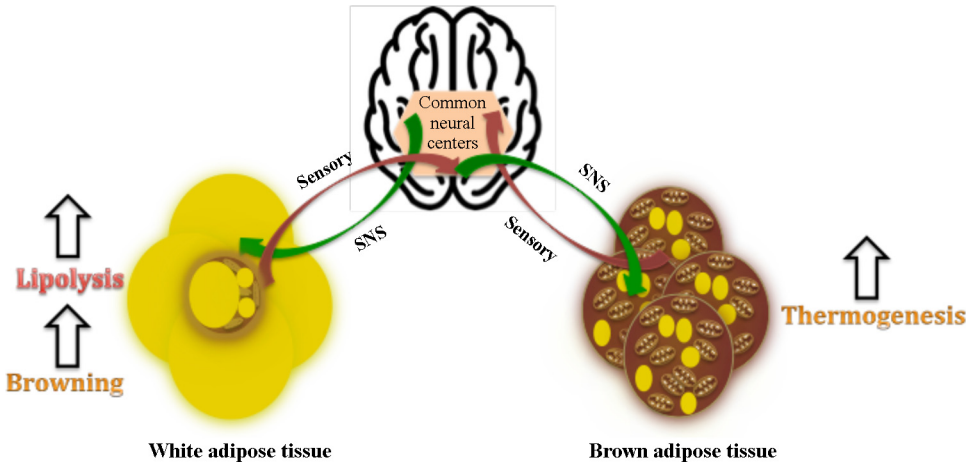

Fig. 3. Sympathetic and sensory control of brown adipose tissue (BAT) and white adipose tissue (WAT) depots. Common neural centers involved in the regulation of energy balance have been proposed to relay sympathetic impulses to, and receive sensory inputs from, BAT and WAT depots (132, 133). While sympathetic nervous system (SNS) sensory feedback loop is proposed to be largely responsible for the regulation of lipolysis in WAT and thermogenesis in BAT, emerging evidence indicates that sensory inputs from WAT can alter thermogenic responses in BAT (56).

these factors work either by interacting with or modulating the levels of SNS activity or its downstream effector norepinephrine. Thyroid hormones are well known regulators of adrenergic signaling within brown adipocytes as well as of UCP1 gene expression (120). Mice with targeted disruption of type 2 iodothyronine deiodinase in classic brown adipocytes exhibit impaired BAT function, defective adaptive thermogenesis, and hypothermia on cold exposure (36). Thyroid hormones are also known to influence hypothalamic mechanisms to alter SNS activity to BAT, thereby exerting their control over BAT thermogenesis (95). Hyperthyroidism was also shown to be associated with threefold higher enhanced glucose uptake in BAT in men (86). Recently, thyroid hormones were also shown to regulate cold-induced BAT activity in a study involving thyroid carcinoma patients (21).

Atrial and B-type natriuretic peptides (NPs), secreted by the human heart during pressure-related changes such as heart failure, have been shown to induce browning and enhance BAT thermogenesis in rodents (97). Cold exposure was associated with increased levels of circulating NPs, whereas coadministration of ANP and β_3-AR was associated with additive effects on browning of white adipocytes, indicating the synergy between SNS and the NP system in regulating beige fat development (97). Enhanced expression of NP receptors, along with an upregulation of browning in gonadal WAT, was also reported recently in a rodent model of Roux-en-Y gastric bypass surgery (108). Central glucagon-like peptide 1 agonism was recently shown to enhance TG-derived fatty acids and glucose uptake by BAT and induce browning of WAT in a rodent study, via an increase in SNS activity to both iBAT and subcutaneous WAT, indicating a plausible role for gut-mediated regulation of BAT and beige fat depots (79). Skeletal muscle is also known to secrete multiple factors during exercise or cold-induced shivering that are known to influence BAT thermogenesis. Irisin, expressed and secreted primarily by skeletal muscle but also by adipocytes, has been shown to induce browning of WAT in rodents by its direct action on adipocytes (16). However, data around its role in human physiology have been questioned and need further exploration (73, 167). Meteorin-like (122) is yet another myokine that has been shown to induce browning of WAT. Its mode of action involves stimulation of eosinophil-mediated type 2 signaling that leads to an accumulation of alternatively activated-type macrophages known to regulate browning of WAT via local release of norepinephrine (122). In addition, multiple other myokines and adipokines, such as myostatin (139), follistatin (17), IL-6 (117), β-aminoisobutyric acid (127), and fibroblast growth factor 21 (51), have been shown to regulate browning of WAT in rodent models. Other circulating factors, such as bone morphogenetic protein (BMP) 4 (119), BMP7 (152) (111), and BMP8b (172), and metabolites, such as lactate (27), ketone bodies (27), and bile acids (49), have been shown to induce browning in rodent studies and in humans (20). A detailed account of various endogenous factors involved in the regulation of BAT and beige biology has been covered by recent reviews (28, 164).

PHYSIOLOGICAL RELEVANCE OF BROWN AND BEIGE FAT

The current interest in BAT biology is essentially underscored by its significant energy-expending capacity that is evident from numerous rodent studies. An increase in BAT metabolic activity has been shown to be associated with reduced body fat, enhanced insulin sensitivity (16), and a cardioprotective lipoprotein profile in rodents (6). In addition, BAT activity was recently shown to be associated with a protective atherosclerosis outcome in a rodent study (11). Besides BAT, physiological benefits of beige fat have also been suggested based on rodent studies (16, 143). However, it is rather difficult to separate the physiological impact of beige fat from BAT in rodents, since most paradigms used for activating beige fat invariably also activate BAT. Few studies using unique approaches, such as unilateral denervation of BAT (136) or use of adiponectin-specific PRDM16 knockout mice (42) that possess dysfunctional beige fat, nonetheless point toward a role for beige fat in regulating whole body metabolic homeostasis. Genetic variability in the beige fat prevalence among rodent models and their propensity to develop obesity is also often cited as an indication for this depot to be playing a significant role in regulating energy balance (62, 176). The role of beige fat in total energy expenditure, however, needs to be better understood, as not every beige depot seems to significantly contribute to total energy expenditure. The archetypical beige depot (i.e., iWAT) in laboratory rodents adapted to cold (thus exhibiting iWAT browning) appears to respond trivially to an acute adrenergic stimulation compared with iBAT (82) (Fig. 4).

Human BAT and Energy Expenditure

Retrospective observations made in multiple studies have reported a negative relationship among BAT presence and BMI, as well as total fat mass in humans (114, 134, 158). Indeed, the tremendous ability of BAT to shift the energy balance equation toward the negative in rodents is a promising utility for human energy metabolism as well, especially in relation to combating obesity and diabetes. As a result, multiple studies have looked at the potential contribution of BAT to whole body energy expenditure. In an historic study, Rothwell and Stock (130) had predicted that 40–50 g of maximally stimulated BAT could contribute to 20% of daily energy expenditure in humans, which, however, seems to be an overestimation. Correcting for allometric differences and likely submaximal state of BAT activity under physiological settings, it was more recently estimated that 50 g of active BAT could contribute to 2.7–5% of basal metabolic rate (157). Since then, a number of controlled cold-exposure studies in acute settings (from 2 to 8 h of cold exposure) have revealed that human BAT is, nonetheless, capable of making significant contributions to the resting energy expenditure (from 13 to 80%) (33, 113, 158, 179).

Despite the initial reports of BAT prevalence to be in the range of 2–7% (31, 114) when assessed in the retrospective settings, BAT prevalence was found to be much higher, ranging from 30 to 100%, in dedicated prospective cold-exposure studies (15). In terms of mass, 0–200 g of BAT can be found in humans across the range of age, BMI, and diabetes (15). Indeed, mass and prevalence of BAT are lower and often below the detection level by ^{18}F-FDG-PET/CT in obese, aged, and diabetic individuals (112, 113, 134, 162). In addition, blood flow to human BAT under stimulated conditions has been estimated to reach 1/50 of what is seen in the case of rodent BAT (121) (Fig. 4). Thus it is clear that our ability to

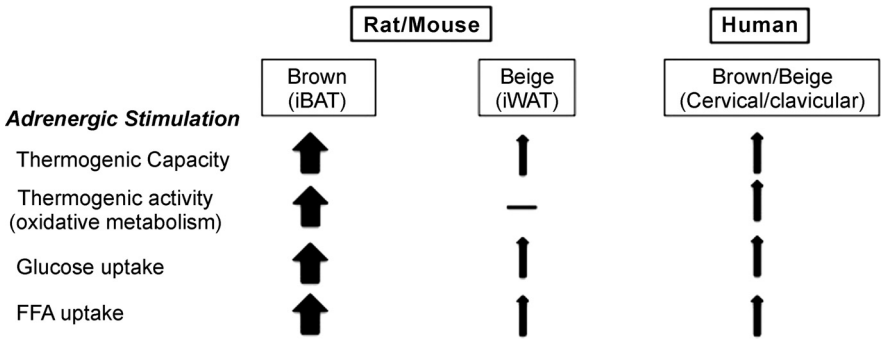

Fig. 4. Physiological relevance of brown and beige fat. Adrenergic agonism (cold exposure) is the strongest known stimulator of brown fat in rodents and humans. Multiple studies covered in the respective section indicate that adrenergically stimulated BAT exhibits significant thermogenic capacity and activity, in association with glucose and FFA uptake. This metabolic activity further contributes to significant increases in energy expenditure in rodents and to a lesser extent in humans. Beige fat, in comparison, has been shown to exhibit dramatic fold-induction in its thermogenic capacity upon adrenergic stimulation relative to its basal state (82). Glucose and FFA uptake also occurs in beige fat; however, this was not associated with any detectable metabolic activity in rodent iWAT, questioning its contribution to whole body energy expenditure (82). In humans, detectable brown fat exhibits glucose and FFA uptake, as well as significant metabolic activity on adrenergic stimulation (113, 154). Human brown fat largely expresses beige markers; however, classic brown fat signatures are also detectable in this depot (46, 74, 93, 106, 142). Note: Arrows are not drawn to reflect on the exact proportional relevance of brown and beige in rodent and human.

recruit BAT remains an imperative aspect of being able to utilize its thermogenic potential in therapeutic settings eventually. Chronic cold-exposure studies have revealed that BAT in humans can be recruited and stimulated to enhance its thermogenic activity (14, 154). Daily mild (15–16°C for 6 h/day for 10 days) (154) or stronger (10°C for 2 h/day for 4 wk) cold exposure (14) was associated with an increase in BAT volume and NST (154), as well as in its oxidative capacity in healthy subjects (14). Daily mild cold exposure at 17°C for 2 h/day for 6 wk was also seen to enhance metabolic activity in men with low BAT activity, which was further associated with a reduction in their body fat mass (178). Yet another study revealed the thermal plasticity of BAT, where both recruitment and involution of BAT activity could be observed in five healthy individuals in a protocol involving multiple temperature variations (90). In addition, appreciable recruitment of BAT has also been reported in older, metabolically healthy obese individuals upon cold acclimation (65).

Human BAT and Glucose Metabolism

As discussed earlier, besides intracellular TG stores, BAT is known to take up circulating glucose to fuel thermogenesis under stimulated conditions. Thus BAT can play an important role in whole body glucose metabolism (Fig. 4). Cold exposure has been shown to induce significant glucose uptake in BAT (6, 82), whereas BAT transplantation in abdominal visceral adipose tissue has been associated with improved glucose tolerance and insulin sensitivity in rodents (149). In concordance, retrospective human studies have reported lower prevalence of BAT in individuals with diabetes and hyperglycemia (112, 114). Prospective studies have further reported that human BAT exhibits enhanced glucose uptake during acute and chronic cold-exposure settings (14, 113), with glucose uptake being affected by intracellular TG pool of BAT, as opposed to its metabolic activity (14). Insulin has also been shown to enhance glucose uptake in human BAT without the associated increase in blood flow that is generally observed during cold exposure (112). However, yet another study reported enhanced whole body glucose disposal in fasted and insulin-stimulated states during cold exposure (5–8 h) in BAT-positive individuals relative to BAT-negative subjects, indicating that BAT contributes to whole body glucose homeostasis and insulin sensitivity (33). In addition, this study makes the case for direct glucose utilization by BAT for thermogenesis upon prolonged cold exposure (33). A link between insulin resistance and BAT activity, independent of age and obesity, was also recently demonstrated in a study where glucose uptake in BAT was reduced upon cold exposure in healthy subjects made insulin resistant after prolonged fasting (66). Reduced glucose uptake observed in this study was not due to lower glucose availability to BAT but was due to the reduced cellular uptake of glucose by BAT, which was further associated with reduced NST and lower core body temperature in these subjects (66), indicating that BAT, like other tissues, becomes insulin resistant, thereby limiting its ability to execute NST and contribute to thermoregulation. Older overweight men with diabetes were recently reported to exhibit lower BAT volume, reduced glucose uptake per volume, reduced perfusion and whitening of BAT, while maintaining their NEFA uptake and oxidative capacity during acute cold exposure (12).

Human BAT and Lipid Metabolism

Besides glucose, BAT can utilize circulating NEFA as well as fatty acids derived from TRLs to fuel thermogenesis (Fig. 4). In fact, BAT was reported to be the primary site for lipoprotein uptake and TG metabolism during acute extreme (4°C) cold exposure (6), which contributed to the clearance of nearly one-half of ingested TG in a rodent study (105). Although BAT has been shown to exhibit NEFA uptake during cold exposure, this has been estimated to be roughly at 0.25% of total NEFA turnover in humans (113). Instead, cold exposure has been primarily associated with utilization of intracellular TG stores as the radiodensity of BAT increased after 3-h cold exposure (113). Whether prolonged cold exposure changes this equation remains to be seen. However, chronic cold acclimation of subjects (i.e., 10°C for 2 h/day for 4 wk) was associated with a reduction in BAT radiodensity, supporting the concept that BAT serves as a substrate sink for circulating glucose and NEFA that are utilized to restore its intracellular lipid stores for an eventual thermogenic output

(12). In this context, WAT lipolysis has been reported to be directly proportional to the oxidative capacity of BAT (12). Although none of the studies have directly investigated TRL uptake by human BAT, a role for BAT in human lipid metabolism can be supported by the observations made in recent studies (33, 35). An increase in the volume and ^{18}F-FDG uptake in BAT after 5–8 h of cold exposure was associated with whole body lipolysis, whole body fat oxidation, and TG-FFA cycling, as well as adipose tissue insulin sensitivity in these studies, indicating that BAT activity may directly or indirectly contribute to lipid mobilization in humans (33, 35). Interestingly, 1 day after cold exposure, circulating levels of TG and very-low-density lipoprotein were found to be lower compared with the levels seen in participants kept at thermoneutral conditions (35). Our laboratory has also reported a positive relationship between UCP1 mRNA levels in human epicardial adipose tissue with circulating high-density lipoprotein-cholesterol levels that would support a role for BAT and beige fat depots in the regulation of whole body lipid metabolism in humans (30).

Human Beige Fat and Metabolic Benefits

An important question of whether beige fat can be recruited or if it can contribute to whole body energy expenditure in humans leads to an interesting discussion. Knowing that the supraclavicular fat depot that is commonly studied for its metabolic activity using radioactive tracer techniques in humans largely exhibits a molecular profile consistent with rodent beige fat (46, 74, 93), one can predict a significant role for beige fat in human energy metabolism. However, when one looks at this depot as the "BAT" depot of the human body and then addresses the relevance of rodent-like beige fat, one notices that most studies report no evidence for browning or metabolic activity in other subcutaneous fat depots under various cold exposure paradigms (65, 90, 154). A recent study involving burn victims, however, reported significant upregulation in UCP1 as well as in the browning aspect of human subcutaneous fat (144). Browning of subcutaneous fat was also associated with enhanced energy expenditure in this study. However, percent contribution of beige fat to total energy expenditure (7%) was estimated to be comparable to BAT (6.3%), in an individual with 100 g of BAT and 15 kg of WAT (118). It is important to underscore that burning is associated with severe adrenergic stress that leads to hypermetabolism (174), thus it is clear that browning of most subcutaneous fat depots in humans requires a much stronger adrenergic stimulus than what is normally generated with cold exposure. Indeed, browning of visceral adipose tissue has been observed in patients with phaeocytochroma (54). An alternative view on this observation may also be put forward in terms of the hypothesis that neural centers involved in thermoregulation may exert inhibitory control over beige fat thermogenesis when functional bona fide BAT depot (for instance iBAT) is present during a thermogenic stress to avoid hyperthermia. Indeed, in mice, unilateral SNS denervation of iBAT has been shown to induce compensatory upregulation in the induction of beige fat (136). In one of our own recent study utilizing radioactivity tracers, maximum metabolic activity was found to be located in the classic BAT on cold exposure as well as after a β_3-adrenergic agonist treatment, indicating that, at least in the presence of classic BAT depot, beige fat exhibits near negligible metabolic activity in rodents (82) (Fig. 4).

SECRETORY RELEVANCE OF BROWN AND BEIGE FAT

In addition to the changes in total body energy expenditure and substrate turnover, metabolic benefits of active BAT and beige fat can also be ascribed to a growing list of molecules that are secreted by these fat depots (163). Some of these molecules act in an autocrine/paracrine role to facilitate either their thermogenic capacity or activity, whereas others act in an inhibitory manner, likely to maintain overall thermogenic homeostasis. For instance, in rodents, BAT is known to secrete nerve growth factor known to enhance its own proliferation by enhancing SNS activity (109), vascular endothelial growth factor known to promote angiogenesis, and perfusion needed for thermogenic substrate flow and heat dissipation (150). Prostaglandins (E_2 and I_2) have also been shown to induce browning of WAT in an autocrine fashion (55, 161). Besides, BAT can release factors like fatty acids, adenosine (59), nitric oxide (58, 126), and BMPs (99, 111, 172) that act on BAT and beige fat to promote their thermogenic activity. In contrast, factors such as soluble form of LDL receptor (173) and endocannabinoids (80) secreted by BAT under stimulated conditions serve to inhibit BAT thermogenesis.

BAT and beige fat are also known to secrete factors with endocrine features, thereby supporting the idea that these fat depots can exert regulatory control over other organs involved in metabolic homeostasis. Among these, fibroblast growth factor 21, interleukin 6, neuregulin (170), insulin-like growth factor binding protein 2 (18), retinol binding protein 4 (128), and angiopoietin-like protein family member 8 (177) have been reported to target liver, pancreas, and bone, along with the adipose tissues to improve whole body insulin sensitivity (163). In this context, no specific factors exclusively expressed by beige fat over BAT have been identified so far. Similarly, our understanding of the human BAT and beige secretome is at the preliminary stages, as no factor has thus far been identified as being uniquely secreted by either of these depots in humans. Transplantation of human beige adipocytes in murine models has, nonetheless, been shown to improve insulin sensitivity (98), reflecting on the potential of putative "beigo-kines" or "BATo-kines" in improving metabolic homeostasis in humans (163).

DETECTION OF HUMAN BAT: LIMITATIONS AND ISSUES

It is without doubt that much of the progress made in our understanding of human BAT comes from ^{18}F-FDG uptake studies done in both retrospective and prospective settings. However, the technique and its data interpretation are not without limitations. Study of BAT in humans has various facets, including investigation of its presence, volume, and metabolic activity. A variety of factors at the individual level, such as age, sex, metabolic condition, and ethnicity, as well as means used for activation, scanning, and reporting BAT presence and activity contribute to the variability observed in human BAT studies. Apart from technical issues related to volume estimation by PET/CT, brown fat in humans generally is very heterogeneous, being a mixture of white and brown (or beige) adipocytes, making interpretation of volume data difficult. Recently, a consensus statement was released such that

common methodological considerations can be utilized to identify a more consistent role for BAT metabolism in humans (32). Furthermore, it is important to note that our referral to the presence (and prevalence) of BAT essentially represents positive ^{18}F-FDG uptake in selected areas. However, we acknowledge that lack of ^{18}F-FDG uptake does not necessarily mean lack of BAT in those individuals. The lack of BAT detectability may obviously arise due to lack of BAT stimulation or detection, owing to multiple factors discussed above.

Notably, ^{18}F-FDG measures glucose uptake per se, which is an indirect measure for the metabolic activity of human BAT. While glucose uptake was recently shown to be directly contributing to distinct mobilizable intracellular lipid pool in rodent primary brown adipocytes (72), such demonstration has not been made in humans. Considering that BAT thermogenesis heavily relies on fatty acids, especially those derived from intracellular lipid stores (14, 113), radioactive tracers that use labeled fatty acids (12, 113) likely represent better tools for assessing BAT activity. In addition, acetate (12, 113) and oxygen tracers (102, 112) that allow for the detection of metabolic activity (i.e., ^{15}O-O_2) and perfusion (i.e., ^{15}O-H_2O) of BAT, respectively, serve as better tools in assessing human BAT activity.

Considering that ^{18}F-FDG/PET-CT scanning involves exposure to ionizing radiation, thereby limiting its repeated usage, there is increased need for finding better noninvasive, nonradioactive means to study human BAT. Based on various aspects of BAT physiology, such as its magnetic properties, its heat-generating capacity, and high perfusion rates during metabolic activity, methods such as magnetic resonance imaging (159), infrared thermography (89), and near-infrared spectroscopy (102) have been tested for assessing human BAT, respectively. However, these methods come with their own limitations covered in detail by van der Lans et al. (155). Efforts are needed to find suitable techniques that can overcome these limitations while being available for use by the broader research community.

The variability observed in multiple human studies is often, and correctly so, attributed to the length and extent of cold exposure, as well as the methodology and criteria used to interpret ^{18}F-FDG signals. Since ^{18}F-FDG measures glucose uptake and fatty acids are most likely the main energy source, it is difficult to actually translate the ^{18}F-FDG-PET/CT data toward tissue-specific energy expenditure. Second, apart from technical issues related to volume estimation by PET/CT, the brown fat tissue in humans generally is very heterogeneous, being a mixture of white and brown (or beige) adipocytes, making interpretation of volume data difficult.

CONCLUSIONS AND OUTSTANDING QUESTIONS

Recent advances made using imaging studies have clearly established the presence of BAT in humans and have brought its thermogenic potential to the fore once again. Its immense thermogenic potential, coupled with the discovery of brite adipocytes, which happen to be located in white fat depots in rodents, has truly rejuvenated the adipose tissue field, where we now seek to understand the mechanisms involved in their development, proliferation, and thermogenic activity. Whereas brite adipocytes retain their thermogenic potential much like the classic brown adipocytes, an enhanced understanding of their origin is necessary to ascertain whether we focus on converting white adipocytes into brown adipocytes or look for bona fide brite precursors and/or white-looking brite adipocytes. Rodent studies have further demonstrated a clear potential for BAT and beige thermogenesis in ameliorating obesity, diabetes, and atherosclerosis (11, 31, 76). Multiple human studies discussed above have also pointed in the same direction, when we consider the PET-detectable supraclavicular and cervical fat to be the main BAT depot of the body. Once again, whether we focus on recruiting and stimulating this BAT/beige depot or attempt to "brown" additional fat depots, we need to extend our understanding of the local, peripheral, and central control of their thermogenic activity in humans.

Our ability to recruit BAT (14, 65), coupled with observations of preserved BAT oxidative potential, in obese and diabetic individuals seem to be steps in the right direction (12). Reduced blood flow and insulin or catecholamine resistance are proposed to be the plausible factors behind the observations of reduced BAT presence and activity in obese and diabetic individuals (12). Ethnic differences have also been observed in BAT volume and basal resting energy expenditure among humans (3). Focusing on the underlying mechanisms and ways to overcome these limitations may allow us to utilize the full potential of NST in improving the metabolic homeostasis in these populations. Cold exposure has been consistently shown to be effective in improving insulin sensitivity in diabetic individuals (47, 64). It is also known to be the most effective activator of BAT thermogenesis in humans to date (156). A significant role for muscle shivering besides BAT thermogenesis in the beneficial outcomes associated with cold exposure has been implied recently (13, 64). However, most of these studies employ short-term cold exposure protocols. More studies are needed to assess whether long-term cold exposure could shift the relative contribution of BAT and NST in the beneficial outcomes associated with cold exposure toward the heavy side. Indeed, long-term studies are also needed to assess whether activation of BAT thermogenesis is accompanied by an upregulation of compensatory mechanisms to offset enhanced energy expenditure to ascertain the sustainability of BAT-based approaches.

A case has also been made for targeting the browning of visceral fat depots specifically to improve their metabolic function using pharmacological means in humans that may or may not involve enhanced energy expenditure (57). Considering that visceral fat accumulation, cellular hypertrophy, and inflammation are strongly associated with cardiometabolic disease burden (151), enhanced understanding of whether browning can reverse any of these features warrants further investigation in humans. Recent demonstrations that BAT and beige fat secrete factors that are capable of communicating with peripheral organs further point toward their ability to influence whole body metabolic homeostasis (163). An important question of whether their secretome alters during the "active" or "inactive" state or exhibits depot specificity in humans needs to be determined. In conclusion, although it is clear that much work is needed before safe BAT- or beige-based approaches can become a therapeutic reality, thermogenic abilities of BAT and "browned WAT" clearly represent novel and worthy tools to be employed in our arsenal against obesity and metabolic syndrome in humans.

HIGHLIGHTS

1. Rodent studies point toward the tremendous thermogenic potential of brown fat. Its oxidative capacity is detectable as well as recruitable in most adult humans, including obese and diabetic individuals.
2. Two types of brown fat are recognizable in humans and rodents, classic brown and beige, which differ with respect to their cellular origins, molecular markers, anatomic location, and extent of inducibility, yet retain similar thermogenic potential.
3. BAT and beige fat activity is primarily regulated by SNS; however, an increasing number of circulating factors are also being recognized that can influence BAT and beige recruitment and activity, particularly in rodents.
4. Targeting BAT and/or beige could allow us to improve whole body energy expenditure and/or metabolic homeostasis in humans, although their quantitative contribution still remains to be established.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

K.C. drafted manuscript; K.C., W.D.v.M.L., and D.R. approved final version of manuscript; W.D.v.M.L. and D.R. edited and revised manuscript.

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